

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/44, C07D 401/12	A1	(11) International Publication Number: WO 90/09175 (43) International Publication Date: 23 August 1990 (23.08.90)
(21) International Application Number: PCT/SE90/00070 (22) International Filing Date: 2 February 1990 (02.02.90) (30) Priority data: 1/30311 9 February 1989 (09.02.89) JP (71) Applicant (for all designated States except US): AKTIEBOLAGET HÄSSLE [SE/SE]; S-431 83 Mölndal (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : TOMOI, Masaaki [JP/JP]; 3-5-65-1214, Nishi-iwata, Higashi-Osaka City, Osaka 530 (JP). IKEDA, Yoshifumi [JP/JP]; 914-2, Oaza-Nakasoi, Nakatsu City, Oita 870 (JP). YOKOTA, Yoshiko [JP/JP]; 25-8, Wakazono-cho, Ibaraki-shi, Osaka-fu 530 (JP).		(74) Agents: MIKSCHÉ, Gerhard et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH, CH (European patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GB, GB (European patent), HU, IT (European patent), KP, KR, LK, LU, LU (European patent), MC, MG, MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: USE OF OMEPRAZOLE AS AN ANTIMICROBIAL AGENT (57) Abstract Use of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the treatment of infectious diseases, especially such caused by <i>Campylobacter pylori</i> .		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	HU	Hungary	NO	Norway
BJ	Benin	IT	Italy	RO	Romania
BR	Brazil	JP	Japan	SD	Sudan
CA	Canada	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic	KR	Republic of Korea	SN	Senegal
CG	Congo	LJ	Liechtenstein	SU	Soviet Union
CH	Switzerland	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany, Federal Republic of	MC	Monaco	US	United States of America
DK	Denmark				

Use of omeprazole as an antimicrobial agent

5

Field of the Invention

The present invention relates to the new use of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-
10 1H-benzimidazole (generic name: omeprazole) or a salt thereof as an antimicrobial agent and more particularly as an antimicrobial agent, which is particularly active against gram-negative bacteria.

15 Background of the Invention

In view of the abuse or unscrupulous use of antimicrobial drugs in the treatment of infectious diseases or for other purposes and the consequent emergence of drug-resistant
20 strains, increased incidence of microbial substitution due to disturbance of the bacterial flora, changes in profile of infectious diseases, etc., there has been a constant demand for the development of new antimicrobial agents.

25 This application is especially directed to the treatment of infections caused by *Campylobacter pylori*.

Campylobacter pylori is a gram-negative spirilliform bacterium which colonises deeply in the gastric mucosa. Treatment with commonly used antibiotics has given
30 insufficient effect.

Prior art

Omeprazole and its pharmaceutically acceptable salts,
35 which are used in accordance with the invention, are known compounds, e.g. from EP 5129 and EP 124495 and can

be produced by known processes, for example by the process described in Japanese Patent Application No. 34956/1985.

Outline of the invention

5

The intensive research undertaken by the inventors of the present invention for accomplishing the above-mentioned object revealed surprisingly that 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-
10 benzimidazole (generic name: omeprazole) and pharmaceutically acceptable salts thereof, which are known to have gastric antisecretory activity known to be an antiulcer drug have excellent antimicrobial activity as well.

15

Heretofore, it has never been known that omeprazole or any compound analogous thereto has antimicrobial activity.

Predicated on the above finding, the present invention
20 relates to an antimicrobial agent containing omeprazole or a salt thereof as an active ingredient.

The salt of omeprazole is virtually optional in kind but is preferably a pharmaceutically acceptable salt. Examples
25 of such salts include inorganic salts, such as alkali metal salts, e.g. sodium salt, potassium salt etc., alkaline earth metal salts. e.g. calcium salt, magnesium salt etc., ammonium salt, organic salts such as organic amine salts, e.g. trimethylamine salt, triethylamine salt,
30 pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine
35 salt.

The antimicrobial agent according to the present invention is particularly active against gram-negative bacteria, especially microaerophilic bacteria, inter alia bacteria of the genus Campylobacter represented by C. pylori, and can be effectively utilized for the prevention and treatment of infectious diseases due to such bacteria in mammalian animals including man, cattle, horse, dog, mouse and rat, in the control and inhibition of environmental pollution, or as a disinfectant.

10

The antimicrobial agent according to the present invention can be made available in a pharmaceutical formulation comprising one or more active ingredients selected from the group consisting of omeprazole and salts thereof or in a formulation containing optional substances as additives (for example, a carrier).

For the treatment or prevention of bacterial infections, for instance, the antimicrobial agent of the invention is generally administered in the form of a pharmaceutical preparation containing omeprazole as such (i.e. the free base) or a salt thereof as an active ingredient in combination with a pharmaceutically acceptable carrier by the oral, rectal or parenteral route. The carrier mentioned above may be a solid, semi-solid or liquid diluent or a capsule. Compatible dosage forms include various types of tablets, capsules, granules, powders, oral liquids, injections and so on. The proportions of the active ingredient in the total composition is generally 0.1 to 100 weight percent and preferably 0.1 to 95 weight percent. In the case of an injectable preparation, the range of 0.1 to 20 weight percent is particularly preferred. In the case of a preparation for oral administration, the preferred proportion is 2 to 50 weight percent.

In the manufacture of a pharmaceutical preparation for oral administration, the active ingredient can be formulated with a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, starch, amylopectin, a cellulose derivative or gelatin, and a lubricating agent such as magnesium stearate, calcium stearate or polyethylene glycol wax may be further incorporated. The resulting composition is then compressed into tablets. Coated tablets or dragees can be manufactured by coating the core tablets, thus prepared, with a thick sugar solution containing gum arabic, gelatin, talc, titanium dioxide, etc. or a lacquer prepared using a volatile organic solvent or solvent mixture.

Soft gelatin capsules can be manufactured by filling a composition comprising the active ingredient and a known vegetable oil into capsules. Hard gelatin capsules can be manufactured by filling into capsules the granules or pellets each comprising the active ingredient and a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, a cellulose derivative or gelatin.

Preparations for rectal administration are preferably suppositories containing the active ingredient and a neutral oleaginous base, gelatin capsules for rectal administration which contain the active ingredient and a vegetal oil or paraffin oil, and rectal ointments.

Liquid preparations for oral administration can be syrups or suspensions, typically a solution containing 0.2 to 20 weight percent of the active ingredient with the balance being a mixture of sucrose with ethanol, water, glycerol and/or propylene glycol. Optionally, these preparations may additionally contain colors, corrigents, saccharin and, as a thickener, carboxymethylcellulose or the like.

1 Injections can be manufactured in the form of aqueous
2 solutions, typically an aqueous solution containing a
3 pharmaceutically acceptable water-soluble salt of the
4 active ingredient preferably in a concentration of 0.1 to
5 10 weight percent. These preparations may further contain
6 a stabilizer and/or a buffer and may be provided in
7 ampules containing various unit doses.

8 The dosage of omeprazole or a salt thereof depends on
9 individual needs (for example, the patient's condition,
10 body weight, age, sex, etc.) as well as on the method of
11 administration. Generally speaking, the oral dosage may
12 range from 1 to 400 mg as active ingredient per day per
13 adult human and the intravenous dosage may range from 1 to
14 200 mg per day per adult human, and each may be
15 administered in one to a few divided doses.

Pharmacological data

20 Experiment 1

The in vitro antimicrobial activity of the active
ingredient of the present invention was assayed by the
following agar plate dilution method.

25 A loopful (10^7 cells/ml) of the test strain cultured in
Brucella Broth containing 5% of horse serum under 10%
carbon dioxide gas for 2 days was inoculated onto Brucella
Agar containing 5% horse lysed blood. This medium
30 contained a varying concentration of omeprazole. The
inoculated media were incubated at 37°C under 10% carbon
dioxide gas for 2 days and the minimal inhibitory
concentration (MIC) was determined. The result is set
forth in Table 1.

35

Table 1

Test organism	MIC ($\mu\text{g/ml}$)
5 Campylobacter pylori 8005	0.39

EXAMPLES

10

The following examples are intended to illustrate the antimicrobial agent of the invention in further detail and should by no means be constructed as limiting the scope of the invention.

15

Example 1 (25 mg tablets)

Omeprazole	250 g
Lactose	175.8 g
Corn starch	169.7 g

20

The above ingredients are mixed and wetted with 10% gelatin solution, and the wet mixture is sieved through a 12-mesh screen and pulverized. The resulting powder is dried and magnesium stearate is added. This mixture is then compressed into tablets each containing 25 mg of omeprazole.

25

Example 2 (capsules)

	93.5 weight %
30 Carboxymethylcellulose calcium	3.7 weight %
Magnesium stearate	1.9 weight %
Light silicic anhydride	0.9 weight %

The above ingredients are mixed thoroughly and filled into capsules.

35

Example 3 (capsules)

	Omeprazole sodium	93.5 weight %
	Carboxymethylcellulose calcium	3.7 weight %
	Magnesium stearate	1.9 weight %
5	Light silicic anhydride	0.9 weight %

The above ingredients are mixed thoroughly and filled into capsules in the conventional manner.

10 Example 4 (injection)

	Omeprazole sodium	40 mg
	Sterile water to a final volume of 10 ml	

15 The above ingredients are aseptically filled into separate vials to provide an injectable preparation.

Example 5 (capsules)

Pellets without an intermediate layer

20	I - Pulverized mannitol	16150 g
	Dehydrated lactose	800 g
	Hydroxypropylcellulose	600 g
	- Microcrystalline cellulose	400 g
	II - Omeprazole	2000 g
25	Sodium laurylsulfate	40 g
	Disodium hydrogen phosphate	80 g
	- Distilled water for injection	4400 g

30 The dry ingredients (I) are mechanically pre-mixed and, then, a granulated liquid component (II) containing omeprazole is added. The resulting mass is kneaded and moistened to a suitable viscosity. The wet mass is processed by means of an extruder to give spherical pellets which are then dried and screened for size
35 selection.

Intermediate-coated pellets

	Omeprazole pellets without an	
	intermediate layer	6000 g
	III - Hydroxypropylmethylcellulose	240 g
5	- Distilled water	4800 g

Using a fluidized-bed equipment, the polymer solution (III) is sprayed over the pellets without an intermediate layer. In this operation, the spray gun is positioned over
10 the fluidized bed.

Enteric-coated pellets

	Intermediate-coated pellets	500 g
	IV - Hydroxypropylmethylcellulose	
15	phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

20 Using a fluidized-bed equipment, the polymer solution (IV) is sprayed over the intermediate-coated pellets using a spray gun positioned over the bed. After drying to a moisture content of 0.5%, the enteric-coated pellets are
25 screened for size selection and filled in 225 mg portions into hard gelatin capsules. (The above amount corresponds to 20 mg of omeprazole). Thirty capsules thus manufactured are packed into a tight container together with a desiccant.

CLAIMS

1. Use of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or a
5 pharmaceutically acceptable salt thereof for the
manufacture of a medicament for the treatment of
Campylobacter infections.
2. A method for the treatment of Campylobacter infections
10 comprising administering to a patient suffering therefrom
an amount of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or a
pharmaceutically acceptable salt thereof sufficient for
the treatment of said infection.
- 15 3. A pharmaceutical preparation for use in the treatment
of Campylobacter infections wherein the active ingredient
is 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or a
20 pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/SE 90/00070**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: A 61 K 31/44, C 07 D 401/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System		Classification Symbols
IPC5	A 61 K; C 07 D	
Documentation Searched other than Minimum Documentation: to the extent that such Documents are Included in the Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	SE, A, 8600742-4 (AB HÄSSLE) 1 September 1986, see especially pages 9-12	1
X	--	3
A	EP, A, 0045200 (THE UPJOHN COMPANY) 3 February 1982, see especially pages 1 and 8	1
X	--	3

<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search:		Date of Mailing of this International Search Report
19th April 1990		1990 -04- 23
International Searching Authority		Signature of Authorized Officer
SWEDISH PATENT OFFICE		Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 2 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body, see PCT rule 39.1 (iv).

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 90/00070**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
28/02/90

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
SE-A- 8600742-4	86-09-01	NONE	
EP-A- 0045200	82-02-03	DE-A- 3176664	88-04-07
		JP-A- 57053406	82-03-30
		US-A- 4359465	82-11-16